UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/413,785	10/07/99	MANOLAGAS S	D6156

HM12/0918

SHERRY M. KNOWLES, ESQ
KNG & SPALDING
191 PEACHTREE STREET
ATLANTA GA 30303-1763

EXAMINER	
STROUP, C	
ART UNIT	**PAPER NUMBER**
1633	7

DATE MAILED: 09/18/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

12/19/00
112,1 not applicable. Amendment A recites PTH 1-34 + not just a PTH fragment.

Office Action Summary

Application No.	Applicant(s)
09/413,785	Manolagas et al
Examiner	**Group Art Unit**
Stroup, Carrie	1633

☐ Responsive to communication(s) filed on _____

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) 1-24 is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-24 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 3

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Applicant's amendment Paper 6, filed 6/30/00, has been entered. Claims 11-7, 9-14 have been amended, and claims 15-24 have been added. Claims 1-24 are currently pending in the present application.

The numbering of claims is not in accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When new claims are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not).

Misnumbered claim 24 been renumbered 23.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-5, 15, 16, 20-22, and 23 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant's claimed invention is to a method of increasing the lifespan of osteoblasts in a host by administering a parathyroid fragment "wherein said parathyroid fragment is to said host" (claim 1). The specification discloses the use of bPTH (1-34), bovine parathyroid hormone consisting of from the first to the thirty fourth amino acid of PTH, for inhibiting the apoptosis of osteoblasts in vivo. The specification fails to disclose, though, other fragments of

PTH which also inhibit apoptosis of osteoblasts in vivo, or the methods of determining such. The specification does not indicate what distinguishing feature, other than inhibition of apoptotis in osteoblasts, are shared by members of this genus of fragments. Thus, the scope of the claims include numerous structural variants, and the genus is highly variant because a significant number of structural differences between genus members is permitted, yet the specification does not provide guidance as to specific changes to make. Structural features that could distinguish compounds with implants in the genus from others in the protein class are missing from the disclosure. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, such as which specific protein domains confer inhibition of osteoblast apoptosis , and because the genus is highly variant, the ability to inhibit apoptosis is insufficient to describe the genus. One of skill in the art would reasonable conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, applicant was not in possession of the claimed genus.

3. Claims 1-5, 15, 16, 20-22, and 23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of increasing the lifespan of osteoblasts in a bone-containing host by administering the PTH(1-34) specific to each host, does not reasonably provide enablement for a method of increasing the lifespan of osteoblasts in a bone-containing host by administering a parathyroid fragment that is the parathyroid hormone to said host. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. .

As stated on page 2 of this Official action, the specification fail to disclose the identity and method of use of a parathyroid fragment, other than PTH(1-34), nor the method of isolating other parathyroid fragments which confer the

ability to inhibit apoptosis of osteoblasts in vivo. Therefore, it would require undue experimentation by one of skill in the art to ascertain which specific fragments of a parathyroid hormone per type of species provided the biological activity of inhibiting osteoblast apoptosis.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

5. Claims 7, 9, 11, 12, 14, and 17- 19 are rejected under 35 U.S.C. 102(a) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Weinstein et al (7/1998).

Applicant's claimed invention is to a method of screening for a compound that reduces bone loss by treating the osteoblast cells with glucocorticoid, contacting them with a test compound in vitro (claim 12) or in vivo (claim 19), measuring the number which undergo apoptosis, and comparing such to control cells which were also treated with glucocorticoid. The claimed invention also includes a method of evaluating whether a compound stimulates bone formation *comprising* the steps of administering the test compound to a bone-containing host, determining the number of osteoblasts which undergo apoptosis, and comparing them to the control cells.

Weinstein et al disclose the administration of prednisolone, a synthetic glucocorticoid analogue, to mice to determine the effects of excess glucocorticoids on bone cells, wherein bone densitometry, bone heistomorphometric analysis, detection and quantification of osteoblasts in ex vivo cultures, and measurements of osteoblasts apoptosis was conducted (e.g., pgs 275-276). Results indicated that excess glucocorticoid induce apoptosis threefold in osteoblasts derived from cancellous bone (pg 279, col. 1). In light of Weinstein, it would have also been obvious to use an animal model to test for compounds which counter the adverse apoptotic inducing effect of glucocorticoids and to use in vitro assays for exposing osteoblasts to glucocorticoids to test its effect on the apoptosis of said cells because in vitro assays for measuring cell apoptosis were widely known in the art at the time of the invention (Paper 2, filed 12/23/99, page 10). Therefore, the claimed invention was anticipated.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 8 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weinstein et al (7/1998) as applied to claims 7, 9, 11, 12, 14, and 17-19 above, and further in view of Jilka et al (1996).

Applicant's claimed invention further includes the use of SAMP6 and SAMR1 mice in the claimed methods of claims 11 and 17.

As noted in Paper 6, filed 6/30/00, page 6-7, the use of SAMP6 and SAMR1 mice was widely known and used in the art at the time of the invention to model ostepenia, wherein SAMP6 exhibited impairment of osteoblast formation associated with decreased bone formation and decreased bone mineral density. Therefore, it would have been obvious to one of ordinary skill in the art to also use said mice for use in the claimed invention for testing the effect of compounds on the inhibition of apoptosis of osteoblasts because the mice were already used as models for measuring the decrease in bone formation, which can result from osteoblast apoptosis.

8. Claims 6 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hill et al (9/1997) in view of Schwartz et al (1992) and Kato et al (12/1997).

Applicant's claimed invention is to a method of screening for a compound that stimulates bone formation comprising contacting osteoblasts cells, such as MLO-Y4, MC3T3-E1, and MG-63 with a test compound, and determining the number of cells undergoing apoptosis versus the control cells.

Hill et al teach an in vitro assay for testing calvarial osteoblasts with multiple growth factors, cytokines, and osteotrophic hormones to determine their effect on the apoptosis of the osteoblasts. Test compounds that resulted in a reduced rate of apoptosis as compared with the control were thus shown to also facilitate bone formation (see entire article.) Hill et al does not teach the use of specific osteoblasts cell lines, such as MLO-YA, MC3T3-E1, and MG-63.

Schwartz et al teach that MC3T3-E1 and MG-63 are osteoblast cell lines which are routinely utilized in in vitro assays (abstract).

Kato et al teach that MLO-Y4 is the murine long bone osteophyte Y4, with properties similar to primary osteophytes and is appropriate for use in in vitro assays to study osteophyte activity.

In light of Hill, Schwartz, and Kato et al it would have been obvious to one of ordinary skill in the art to modify the assay of Hill et al by incorporating the use of any osteoblast or osteophyte cell line, such as MLO-Y4, MC3T3-E1, and MG-63. One would be motivated to do this because the routine use of said cell lines for in vitro assays indicates to the artisan the likelihood of success in their use of testing the inhibition of apoptosis, or any other in vitro assay. Additionally, and as previously stated in Paper 2, filed 12/23/99, page 10, the assays for apoptosis of claim 10 were routinely known and widely used in the art at the time the invention was made, therefore one of ordinary skill in the art would readily have been motivated to incorporate their use in the claimed invention.

No claim is currently allowed. It is noted, though, that the method of increasing the lifespan of osteoblasts in a host, to include humans, by administering hPTH(1-34) is enabled by the prior art which had previously administered hPTH (1-34) to increase bone mass (Finkelstein et al, *JAMA*, 9/1998, 280(12): 1067-1073; Reeve et al, *Brit. Medical J,* 6/1980, pg 1340-1344)

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carrie Stroup whose telephone number is (703) 306-5439. The examiner can normally be reached on Monday through Friday from 8:30 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached at (703) 308-0447. The fax phone number for this Group is (703) 308-0294.

Carrie Stroup

JOHN L. LeGUYADER
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

L8 ANSWER 19 OF 20 MEDLINE DUPLICATE 16

AB Both 1,25-(OH)2D3 and prostaglandin E2 (PGE2) stimulate alkaline phosphatase activity in MC-3T3-E1 cells. Previous studies, demonstrating a correlation between 1,25-(OH)2D3-dependent alkaline phosphatase and phospholipase A2 activities in matrix vesicles isolated from growth cartilage chondrocyte cultures, suggest that one mechanism of vitamin D action may be via autocrine or paracrine action of PGE2. Since most PGE2 is derived from arachidonic acid released by the action of phospholipase A2, we examined whether 1,25-(OH)2D3 stimulates phospholipase A2 activity in three **osteoblastic cell lines**: ROS 17/2.8 cells, MC-3T3-E1 cells, and **MG-63** cells. 1,25-(OH)2D3-dependent alkaline phosphatase and phospholipase A2 activity were correlated with production of PGE2 and PGE1 in the MC-3T3-E1 cells. Alkaline phosphatase specific activity was enriched in the matrix vesicles produced by all three cell types and was stimulated by 1,25-(OH)2D3 at 10(-8) to 10(-7) M. Although phospholipase A2 specific activity was enriched in the matrix vesicles produced only by the ROS 17/2.8 cell cultures, stimulation of this enzyme activity was observed only in the MC-3T3-E1 cell cultures. The effects of 1,25-(OH)2D3 on phospholipase A2 were dose-dependent and were significant at 10(-8) to 10(-7) M. There was a significant increase in PGE2 production in the MC-3T3-E1 cell cultures only. Indomethacin reduced PGE2 production to base line values. Even at baseline, MC-3T3-E1 cells produced ten times more PGE2 than did the ROS 17/2.8 or **MG-63** cell cultures. The effects of 1,25-(OH)2D3 on PGE1 were comparable to those on PGE2.(ABSTRACT TRUNCATED AT 250 WORDS)

AN 92256058 MEDLINE

DN 92256058

TI Differential regulation of prostaglandin E2 synthesis and phospholipase A2 activity by 1,25-(OH)2D3 in three osteoblast-like cell lines (MC-3T3-E1, ROS 17/2.8, and **MG-63**).

AU Schwartz Z; Dennis R; Bonewald L; Swain L; Gomez R; Boyan B D

CS University of Texas Health Science Center, San Antonio 78284.

NC DE-05937 (NIDCR)
DE-08603 (NIDCR)
DE-08869 (NIDCR)

SO BONE, (1992) 13 (1) 51-8.
Journal code: ASR. ISSN: 8756-3282.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 199208